59. A composition effective to inhibit cellular proliferation comprising a first compound which is at least three times more potent an activator of a Retinoid X Receptor than a Retinoic Acid Receptor in a co-transfection assay in combination with a second compound which affects cellular proliferation or is a cell-cycle modulator.

60. A composition according to claim 59, wherein the inhibition of cellular proliferation achieved by said composition at a given concentration is greater than the additive effect achieved by using each of the first and second compound alone at said concentration.

61. A composition according to claim 59, wherein the second compound is selected from the group consisting of interferon, methotrexate, fluorouracil and ARA-C.

REMARKS

The specification has been amended at pages 78 and 88 to correct typographical errors.

Claim 4 has been amended to correct a typographical error. Applicants do not understand there to be any objection to or rejection of compound claims 4-7 stated in the Office Action, believe claims 4-7 to be in condition for allowance, and therefore request allowance of those claims.

Moreover, since claim 4 is a generic claim, which applicants submit is allowable, applicants request reconsideration of the withdrawal from consideration of claims 8-13. In response to the restriction/election requirement dated

July 6, 1994, applicants elected the species recited on page 13, lines 28-31, on which claims 1-7 and 14-44 read. Since applicants were required under 37 U.S.C. § 121 to elect a single disclosed specie for prosecution on the merits to which the claims would be restricted if no generic claim were finally held to be allowable, and since applicants believe their generic claim 4 to be allowable, applicants believe the basis for withdrawing claims 8-13 from consideration to be removed, and request decision on the allowability of claims 8-13. Claim 8 and claim 9 each specify a single compound, both of which are included in the group of compounds specified in claim 6. The additional compounds in claims 10-13 are encompassed by generic compound claim 4. Accordingly, applicants respectfully request consideration and allowance of claims 8-13.

Claims 14-32 have been rejected under 35 U.S.C.§ 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim, and accordingly claims 14, 15, 18, 19 and 25-32 have been amended to rewrite them in independent form to overcome the rejection. Claims 16-17 have not been amended since claim 16 is already in independent form, and method claim 17 is dependent on method claim 16. Similarly, claims 20-24 have not been amended to independent form since method claims 20, 21, and 24 are dependent on now independent method claim 19, and method claims 22-23 are further dependent on dependent method claim 21. Claim 21 has been amended only insofar as to specify additional processes, as described at page 83 of the specification. Applicants believe claims 14-32 are now in condition for allowance.

Claims 1-3 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite and overly broad. The Examiner states that the term "a ligand" without specifically

defining the ligand is overly broad. Applicants respectfully traverse this rejection.

In the first instance, applicants are confused concerning the basis of the rejection. Although stated as being based upon the second paragraph of 35 U.S.C. § 112, a premise of the rejection is that the rejected claims are overly broad. As such, the rejection is worded more as a conventional expression of a 35 U.S.C. § 112, first paragraph, rejection rather than a second paragraph rejection. Nevertheless, applicants will proceed on the assumption that the Examiner fully intended the 35 U.S.C. § 112, second paragraph, rejection as formulated.

There are only two grounds upon which a § 112, second paragraph, rejection can be based. As the Board of Appeals pointed out in Ex Parte Ionescu, 222 U.S.P.Q. 537, 539-40 (BPOA 1984), "[i]f the rejection is based on the second paragraph of § 112, the examiner should further explain whether the rejection is based on indefiniteness or failure to claim what the inventor regards as the invention". There are a host of cases which hold that breadth of a claim alone cannot be equated with indefiniteness. See, *e.g.*, Ex Parte Scherberich and Pfeifer, 201 U.S.P.Q. 397, 398 (BPOA 1977)(". . . it is well established that breadth alone does not constitute indefiniteness"); In re Wakefield, 422 F.2d 897, 164 U.S.P.Q. 636, 641 (CCPA 1970)(stating that the fact that claims encompass a very large number of substances doesn't make them indefinite). Claims are definite so long as they "make clear what subject matter they encompass and thus what the patent precludes others from doing." In re Spiller, 500 F.2d 1170, 182 U.S.P.Q. 614, 621 (CCPA 1974). Thus, when the present rejection states that the claims are overly broad, we assume that means that the Examiner contends that the claims cover subject matter which applicants do not

regard to be their invention, the only other basis other than indefiniteness upon which a second paragraph rejection can be made. As we shall show, however, the present claims do assert what applicants regard to be their invention and are definite within the bounds required by the second paragraph of § 112.

Turning now to the specific rejections of claims 1 through 3, the term "ligand" is used in the specification in numerous situations. Therefore, applicants clearly intended that term to express their invention. Accordingly, the claims cannot be considered overly broad by having been directed to subject matter that applicants do not regard as their invention. The term "ligand" is also defined in numerous instances in the specification. For example, at page 3, line 29 to page 4, line 1, the compound all-trans-retinoic acid is identified as a ligand, and specifically a ligand upon which the transcription-modulating activity of Retinoic Acid Receptor-alpha (RAR-alpha) depends. At page 4, lines 8-14, all-trans-retinoic acid is stated to be a natural ligand for RARs and capable of binding those receptors with high affinity, resulting in the regulation of gene expression. At page 5, lines 19-24, the compound 9-cis-retinoic acid is described as a natural endogenous ligand for Retinoid X Receptors (RXRs), able to bind and transactivate the RXRs as well as RARs, and therefore a bifunctional ligand. The term ligand is used elsewhere in the specification, and in claims 1-3, consistent with the above definition.

Applicants therefore submit that the language of claims 1-3 adequately defines the claimed invention with the required reasonable degree of particularity and distinctness and, read in context with the specification, reasonably define and apprise those skilled in the art both of the utilization and scope of what applicants regard as their invention. See, *e.g.*,

Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 624, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985). Specifically, applicants have novelly disclosed in their application the existence of ligands which selectively activate Retinoid X Receptors in preference to Retinoic Acid Receptors, as claimed in claim 1, and/or which modulate a process selectively mediated by Retinoid X Receptors in preference to Retinoic Acid Receptors, as claimed in claim 2. Applicants regard such ligands as their invention, and have disclosed numerous examples of such ligands, as well as clear guidance in the specification on how to predictably and readily identify and assay such ligands to determine and verify the desired activity for the claimed ligands.

Applicants do not seek to claim all ligands, only those ligands which selectively activate Retinoid X Receptors in preference to Retinoic Acid Receptors, and/or which modulate a process selectively mediated by Retinoid X Receptors in preference to Retinoic Acid Receptors. The selectivity characteristic stated in claims 1 and 2 for the ligands of applicants' invention are the best descriptions known to applicants to identify the ligands which applicants regard as their invention, and defines those ligands, with a reasonable degree of particularity and distinctness. Applicants are entitled to claims drawn as broadly as the prior art will allow, and, as we have noted above, breadth alone does not make a claim "indefinite". See also, M.P.E.P. § 706.03(d). Accordingly, applicants request reconsideration and allowance of claims 1 and 2.

Claim 3, which is dependent on claim 2, claims only the narrower subset of ligands which are at least 5-fold more potent an activator of Retinoid X Receptors than of Retinoic Acid

Receptors, a demonstrated characteristic of numerous of the ligands disclosed in the application. This characteristic specifically identifies a subset of ligands which applicants regard as their invention. Accordingly, applicants request reconsideration and allowance of claim 3.

The Examiner has also made a provisional rejection of claims 1-3 as claiming the same subject matter as claims 1-4 in co-pending application Serial No. 141,914 or 141,246, a provisional double patenting rejection. Applicants respectfully traverse this rejection. Claims 1-3 of the instant application claim ligands which exhibit the selective activation properties specified. In contrast, in copending application Serial No. 141,914, claims 1 and 2 are more narrowly directed to compounds having a specified generalized formula, claim 3 is directed to a compound selected from a group of five specific compounds, and claim 4 is directed to a pharmaceutical composition comprising a compound specified in claim 1. There are ligands which would literally infringe claims 1-3 of the instant application, but which would not literally infringe the compounds more narrowly specified in claims 1-3, nor the pharmaceutical composition specified in claim 4, of copending Ser. No. 141,914. See MPEP § 804. Similarly, in copending application Serial No. 141,246, claims 1-3 are narrowly directed to compounds having a specified generalized formula, and claim 4 is directed to a compound selected from a group of 6 specific compounds. There are ligands which would literally infringe claims 1-3 of the instant application, but which would not literally infringe the compounds more narrowly specified in claims 1-4 of copending application Ser. No. 08/141,246. Accordingly, applicants submit that claims 1-3 of the instant application do not claim the identical invention as claims 1-4 of copending Serial No. 141,914 nor

claims 1-4 of copending Serial No. 141,246. See, *e.g.*, In re Vogel, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (CCPA 1970)("invention defined by a claim reciting 'halogen' is not the same as that defined by a claim reciting 'chlorine', because the former is broader than the latter."). Therefore, applicants respectfully request reconsideration and withdrawal of the provisional rejection. In addition, should the provisional rejection become actual, applicants request the further opportunity to address the actual basis for the rejection.

Claims 33-44 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite as failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention and embracing a wider spectrum of compounds than the specification supports. Applicants respectfully traverse this rejection. In doing so, as with claims 1-3 above, applicants will proceed on the assumption that the Examiner fully intended the stated 35 U.S.C. § 112, second paragraph, rejection as formulated (rather than one premised on a § 112, first paragraph, rejection of overly broad claims), and therefore on the assumption that the Examiner contends that the claims cover subject matter which applicants do not regard to be their invention. Claims 33-44 are directed to the disclosed compositions, as well as to methods for using them, comprising the combination of two different ligands -- a first ligand which selectively activates Retinoid X Receptors (RXRs) in preference to Retinoic Acid Receptors (RARs), and a second ligand having the reverse properties of selectively activating RARs in preference to RXRs. The specification discloses such ligands and provides clear guidance on how to predictably select and assay such ligands to verify their claimed activity. The specification also discloses the surprising and greater than additive effect of

combining these two different types of ligands into a composition. Applicants submit that the language of claims 33-44 does define the claimed invention with a reasonable degree of particularity and distinctness which reasonably apprises those of skill in the art both of the utilization and scope of what applicants regard as their invention. Claim 40 has also been amended only insofar as to specify additional processes, as described at page 83 of the specification. Accordingly, applicants request reconsideration and allowance of claims 33-44.

New claims 45-61 have been added with this amendment. Support for these claims is found in numerous places in the specification, including, *e.g.*, for claims 45-46 at pages 67, 69-75; claim 47 at page 83; claim 48 at pages 78-79, 83-84, 88-89; claim 49 at page 83; claims 50-51 at pages 69-75; claim 52 at pages 68-75, 83; claims 53-54 at pages 69-75, 83, 96-100; claims 55-58 at pages 69-75, 83; and claims 59-61 at pages 94-96.

Accompanying this Response and Amendment is our check in the amount of $2940, in part to cover the $2070 fee for the additional claims of this application, as amended. Also accompanying this communication is a petition requesting a three month extension of time to file this Response and Amendment, along with our payment of the $870 extension fee.

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The Commissioner is hereby authorized to charge any additional fees which may be required by this communication, or credit any overpayment, to Deposit Account No. 12-2475.

Respectfully submitted,

LYON & LYON

Dated: August 21, 1995

By: _____
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